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BUPROPION-INDUCED CLIMBING THROUGH D-1 AND D-2 DOPAMINE RECEPTOR ACTIVATION

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ABSTRACT

Intraperitoneal (IP) injection of bupropion (3,6, amine (4,16 mg kg^{-1}) induced dose-dependent climbing in mice. The climbing response induced by both drugs were decreased in animals pretreated either with the D-1 antagonist SCH 23390 or the D-2 antagonist sulpiride. The ∝-adrenoceptor blocker phenoxybenzamine decreased the climbing induced by both bupropion and amphetamine, but the β-adrenergic blocker propranolol and the antimuscarinic agent atropine had no effect. Reserpine pretreatment abolished the climbing induced by bupropion but not that of amphetamine. However, alpha-methyl-p-tyrosine combined with reserpine treatment reduced the amphetamine-induced climbing. It is concluded that both bupropion and amphetamine-induced climbing through release of dopamine and subsequent activation of D-1/D-2 receptors; however, the mechanisms by which dopamine is released by these drugs may differ.

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INTRODUCTION

Bupropion is a compound chemically dissimilar to tricyclic antidepressants and monoamine oxidase inhibitors. The drug is clinically used as an antidepressant drug,[9] whose mechanism of action can not be explained solely on the basis of alteration in presynaptic or postsynaptic receptor-mediated events in monoamine pathways.[5] In comparison with the tricyclics, bupropion is a weaker inhibitor of noradrenaline uptake *in vitro* but is more potent against dopamine uptake.[2] The central actions of bupropion differs from that of the tricyclic antidepressants or of the monoamine oxidase inhibitor class of antidepressants in that bupropion, like dexamphetamine, increases locomotor activity in rodents.[13] There is also evidence indicating that at least some of the central actions of the drug are mediated through dopamine.[1] Previously, we have shown that bupropion induced turning towards the lesion in rats with unilateral 6-hydroxydopamine lesion of the dopamine nigrostriatal pathway.[16] It also has anorectic effects and produces hyperactivity, both of which may be mediated through indirect dopaminergic mechanisms.[17] The purpose of the present work was to study the effect of bupropion in comparison with that of amphetamine o climbing behavior in mice.

MATERIALS AND METHODS

Animals. Male albino mice (25-30 g) were used. They were housed 10 per cage (12 × 24 × 40 cm) at an environmental temperature of 22±2° C and under 12-h dark schedule. Food and tap water were freely available except during the experiments. Each animal was used once only.

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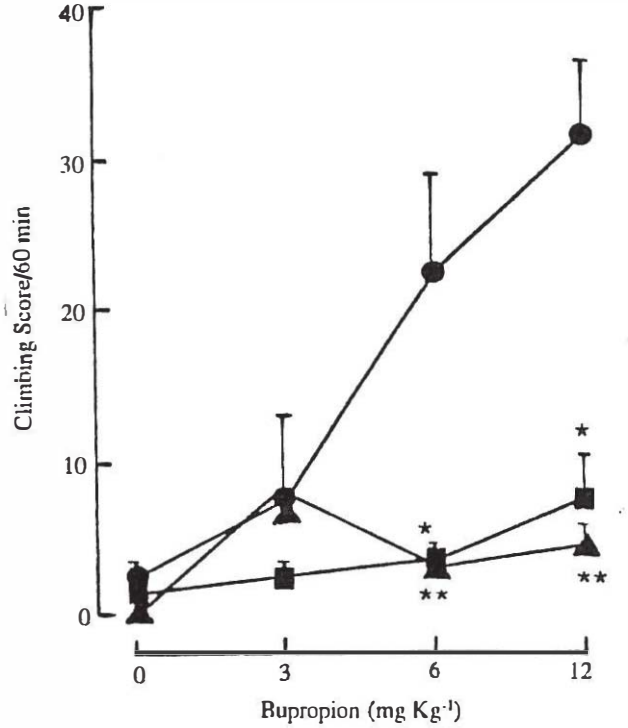

Fig. 1. Climbing behavior induced by bupropion in presence or absence of dopamine antagonists. Mice were injected intraperitoneally (I.P.) with different doses of bupropion (●; 3,6,12 mg Kg^{-1}) alone or with either SCH 23390 (■0.05 mg Kg01, I.P.) 30 min. or sulpiride (▲ mg Kg-1, I.P.) 90 min. prior to bupropion administration. Climbing score was recorded for 60 min. after drug injection. Each point is the mean±SEM of at least 10 mice.
*p < 0.05, **p < 0.001 different from bupropion treated groups.

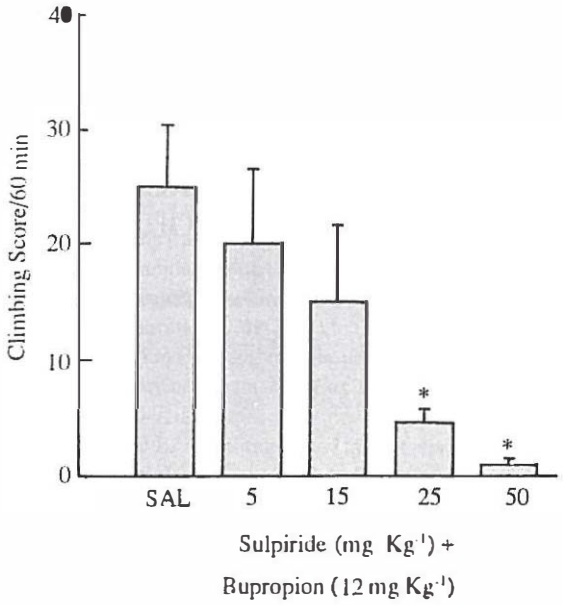

Fig. 2. Effect of different doses of sulpiride on bupropion-induced climbing. Mice were administered bupropion I.P. (12.5 mg Kg^{-1}) either with saline (10 ml Kg^{-1}, I.P.) or with different doses of sulpiride (5, 15, 25, 50mg Kg^{-1}, I.P.) 90 min. before bupropion injection. Each point is the mean±SEM of climbing score/60 min. (n=10).
*p < 0.001 different from saline treated control.

Climbing measurement. The climbing behavior was measured as described before (Zarrindast and Shahed-Dirin, 1990). The animals were put into glass cylinders with a wire mesh wall in a vertical position and allowed to acclimatise for 30 min before drug injection. Climbing was scored as described by Marcais et al.[8] every 2 min. as follows: four paws on the floor, (0); forefeet holding the wall, (1); four paws holding the wall, (2). At each time period, the climbing score±SEM of at least 10 mice during one hour after drug administration are presented.

Drugs. The following drugs were used: bupropion hydrochloride (Wellcome), amphetamine sulphate (SK&F), SCH 23390 (R- (+) -8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-01 maleate; Schering), sulpirde (Delagrange), phenoxybenzamine (SK&F), propranolol (ICI), atropine sulphate (E. Merck), alpha-methyl-p-tyrosine (Sigma) and reserpine (Ciba-Geigy). The drugs were dissolved in distilled water, except for sulpiride and reserpine which were dissolved in 1 drop of acetic acid and then diluted with distilled water, and injected 10 ml/kg.

RESULTS

Effects of D-1 or D-2 dopmine receptor antagonists on climbing induced by bupropion in mice.

Intraperitoneal (I.P.) injection of mice with different doses of bupropion (3,6,12 mg Kg^{-1}) dose-dependently induced a climbing response in mice. The climbing induced by different doses of bupropion was decreased in animals pretreated intraperitoneally with either the D-1 antagonist SCH 23390 (0.05 mg Kg^{-1}, 30 min.) or the D-2 antagonist sulpiride (25 mg Kg^{-1}, 90 min.) (Fig. 1). Pretreatment of animals with different doses of sulpiride (5, 15, 25, 50 mg Kg^{-1}, I.P., 90 min.) reduced the effect of bupropion (12 mg Kg^{-1}) dose-dependently (Fig. 2).

Effects of antimuscarinic, ∝-and β-adrenoceptor blockers on climbing induced by bupropion.

Pretreatment of animals with the ∝-adrenoceptor blocker phenoxybenzamine (5 mg Kg^{-1}, I.P., 60 min.) decreased the climbing response induced by different doses (3,6,12 mg Kg^{-1}, I.P.) of bupropion, but pretreatment

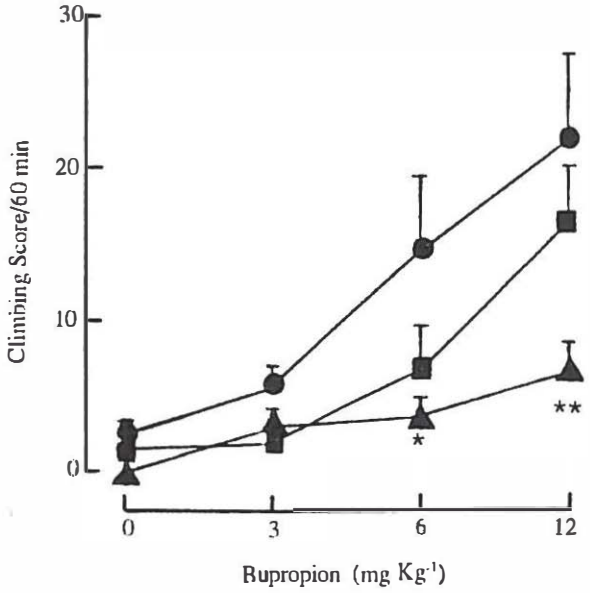

Fig. 3. Effect of ∝-andβ-adrenoceptor blockers on bupropion-induced climbing in mice. Animals were administered different doses of bupropion (3,6 and 12 mg/kg I.P.) in combination with saline (● 10 ml Kg^{-1}, I.P.), phenoxybenzamine (▲ 5 mg Kg^{-1}, I.P.) or propranolol (■10 mg Kg^{-1}, I.P.) 60 min. before bupropion injection. Each point is climbing score for 60 min. (n=10).
*p < 0.05, **p < 0.02 different from saline controls

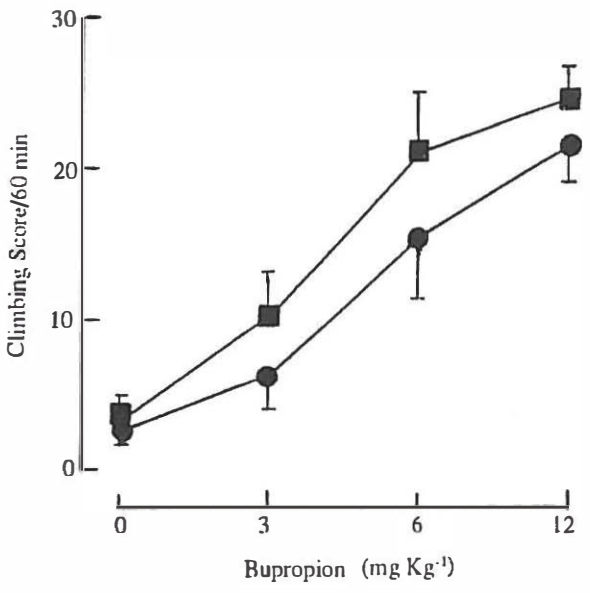

Fig. 4. Effect of atropine on climbing induced by bupropion. Mice were injected different doses of bupropion (3,6,12 mg Kg^{-1}, I.P.) either with saline (● 10 mg Kg^{-1}, I.P.) or atropine (■10 mg Kg^{-1}, I.P) 30 min. before bupropion administration. Each point is the mean±SEM climbing score/60 min. (n=10).

with the B-adrenoceptor blocker propranolol (10 mg Kg^{-1}, I.P., 60 min.) had no effect on the bupropion response (Fig. 3). Atropine pretreatment (10 mg Kg-I, I.P. 30 min.) also failed to alter the climbing induced by bupropion (Fig. 4).

Effects of dopamine receptor antagonists on amphetamine-induced climbing.

Administration of different doses of amphetamine (4,8,16 mg Kg^{-1}, I.P.) induced dose-related climbing in mice. Pretreatment of animals with either SCH 23390 (0.1 mg Kg^{-1}, S.C., 30min.) or sulpiride (25 mg Kg^{-1}, I.P., 90 min.) attenuated the response produced by different amphetamine doses (4-16 mg Kg^{-1}, I.P.) (Fig. 5).

Effects of antimuscarinic or adrenoceptor blockers on amphetamine-induced climbing.

Pretreatment of animals with phenoxybenzamine (5 mg Kg^{-1}, I.P.) but not with propranolol (10 mg Kg^{-1}, I.P.) 60 min. prior to bupropion causes a decrease in climbing scores induced by the drug. Atropine (10 mg Kg^{-1}, I.P., 30 min). pretreatment did not alter the amphetamine (4,16 mg Kg-1, I.P.) effect (Table I).

Effect of reserpine pretreatment on climbing induced by amphetamine or bupropion.

Pretreatment of animals with reserpine (5 mg Kg^{-1}, I.P.,

Table I. The effect of amphetamine in presence or absence of antagonists on climbing behaviour in mice

Treatment	Dose (mg Kg^{-1})	Climbing score/60 min. (mean±SEM)
saline	10 ml	
+amphetamine	4	19.8±5.2
saline	10 ml	
+ amphetamine	16	31.8±5.4
atropine	10	
+amphetamine	4	25.0±4.2
atropine	10	
+amphetamine	16	31.1±5.1
saline	10 ml	
+amphetamine	4	18.6±3.6
saline	10 ml	
+amphetamine	16	32.1±5.9
phenoxybenzamine	5	
+amphetamine	4	5.9±2.1**
phenoxybenzamine	5	
+amphetamine	16	16.5±5.5*
propranolol	10	
+amphetamine	4	24.2±6.2
propranolol	10	
+amphetamine	16	28.6±4.2

Mice were pretreated intraperitoneally with saline, atropine 30 min.or saline, phenoxybenzamine and propranolol 60 min. Before amphetamine administration. Climbing score was recorded for 60 min. after drug injection.
*p

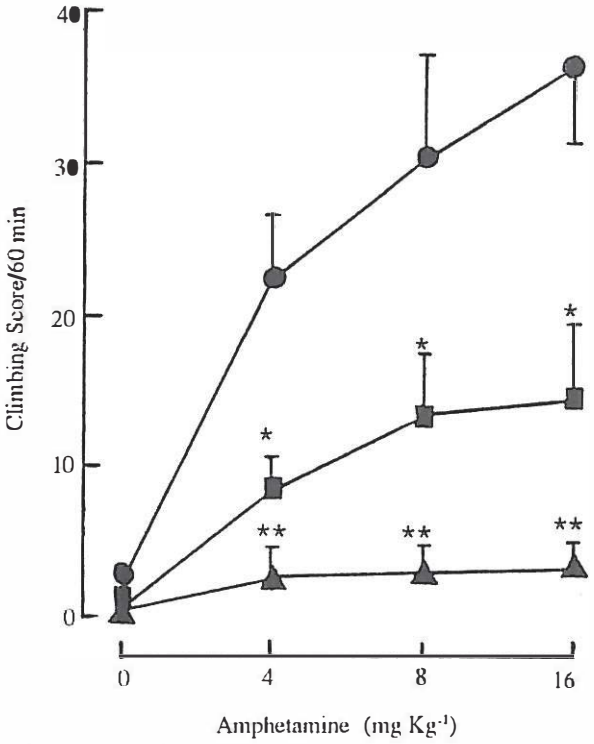

Fig. 5. Effects of dopamine antagonists on climbing induced by amphetamine in mice. Animals were injected with different doses of amphetamine (4,8,16 mg Kg, I.P.) in combination with saline (● 10 ml Kg^{-1}, I.P.), SCH 23390 (■ 0.1 mg Kg^{-1} I.P.) or sulpiride (▲ 25 mg Kg^{-1}, I.P.) before amphetamine administration. Each point is the mean±SEM of climbing score/60 min. (n=10).

*p < 0.001, **p < 0.001 different from saline controls.

18 h) decreased the climbing induced by bupropion (Table II), while the same pretreatment did not alter the response to amphetamine (16 mg Kg^{-1}, I.P.). However in these reserpinized animals employment of alpha-methyl-p-tyrosine (250 mg Kg^{-1}, 1 h) prior to amphetamine reduced the climbing produced by the drug.

Table. II. The effect of reserpine treatment on climbing induced by amphetamine or bupropion in mice

Treatment	Dose (mg Kg^{-1})	Climbing score/60 min. (mean±SEM)
saline+	10	2.6±0.9
amphetamine	4	22.5±4.1†
amphetamine+	16	36.5±5.0†
reserpine	5	
amphetamine	4	32.0±5.1†
reserpine	5	33.5±6.2†
	16	
reserpine	5	
+AMPT	150	
+amphetamine	16	1.0±0.5*
bupropion	12	31.8±4.5†
reserpine	5	
+bupropion	12	0.0±0.0*

Mice were administered intraperitoneally saline, amphetamine and bupropion alone, bupropion in combination with reserpine *18h) and amphetamine in combination with either reserpine (18h) or reserpine (18h) plus alpha-methyl-p-tyrosine (AMPT, 1 h) before the drug injection. Climbing score was recorded for 60 min. after drug injection.

†p < 0.001 different from saline-treated control group.

*p < 0.001 different from amphetamine or bupropion respective control groups.

DISCUSSION

Dose-related climbing was produced by administration of bupropion to mice. It has been shown that activation of D-1 and D-2 receptors by dopaminergic agonists produces cage climbing in mice.[10]

Previously, it has been indicated that bupropion caused anorexia and locomotion[17] and induced ipsiversive turning in rats with a unilateral 6-hydroxydopamine lesion of the dopamine nigrostriatal pathway[16] through a dopaminergic mechanism. The present data demonstrates that pretreatment with either a D-1 antagonist SCH 23390[7] or a D-2 antagonist sulpiride[3,12] reduces the climbing produced by bupropion. These data indicate that climbing induced by bupropion may be mediated through D-1 and D-2 receptor activation. Pretreatment of animals with reserpine, a depletor of cateeholamines, inhibits the climbing induced by bupropion.

It has already been shown that bupropion is a more potent uptake inhibitor of [^{3}H] dopamine than [^{3}H] norepinephrine or [^{3}H] serotonin in nerve endings.[5] These results may therefore suggest the involvement of an indirect dopauninergic mechanism in the bupropion-induced climbing. In the present experiments, it was shown that amphetamine too produces climbing in mice. Amphetamine has been suggested to elicit its effects on locomotion and stereotyped behavior via endogenous catecholamines.[15] The climbing induced by the drug was decreased in animals pretreated with SCH 23390 or sulpiride. Pretreatment of animals with reserpine, however, did not alter the climbing response.

Pretreatment of animals with reserpine plus alpha-methyl-p-tyrosine, an inhibitor of synthesis of catecholamines, completely inhibited amphetamine-induced climbing. Therefore it seems likely that bupropion and amphetamine induce their climbing response through different indirect dopaminergic actions.

It has been hypothesized that indirectly-acting dopamine receptor agonists could be divided into reserpine-sensitive and alpha-methyl tyrosine-sensitive classes.

Dextroamphetamine-like drugs release a small rapidly turning-over pool of catecholamines and its action is blocked by alpha-methyl-p-tyrosine, but not reserpine. On the other hand, the non-amphetamine drugs such as methylphenidate enhance the release of catecholamines and their action is not inhibited by alpha-methyl-tyrosine but is blocked by reserpine.[11] Therefore, bupropion may fall into the methylphenidate class. Pretreatment of animals with the antimuscarinic drug atropine or β-adrenoceptor blocker propranolol did not alter the climbing induced by bupropion and amphetamine. Therefore, the cholinergic or β-adrenoceptor mechanisms are not involved in the climbing response induced by bupropion and amphetamine. When animals were pretreated with the ∝-adrenoceptor blocker phenoxybenzamine, both bupropion-and amphetamine-induced climbing were decreased.

Phenoxybenzamine, a mixed ∝-adrenoceptor blocker has been reported to inhibit dopamine-stimulated adenylate cyclase[14] and also to differentially influence dopamine-induced locomotor and stereotyped behaviors.[4] Therefore although this might partly explain the results obtained, but because of its broad pharmacology, other mechanisms can not be excluded. It may therefore be concluded that both bupropion and amphetamine induce climbing in mice through the indirect activation of D-1/D-2 receptors.

REFERENCES

1. Canning H, Goff D, Leach MJ, Miller A A, Tateson JE. Wheatly PL: The involvement of dopamine in the central actions of bupropion, a new antidepressant. Br J Pharmacol 66:104, 1979.
2. Cooper BR, Hester TJ, Maxwell RA: Behavioral and biochemical effects of the antidepressant bupropion (Wellbutrin): evidence for selective blockade of dopamine uptake in vivo. J Pharm Exp Ther 215: 127-34, 1980.
3. Dichiara G, Proceddu GML, Vargui L, Angiolas A Gessa GL: Evidence for dopamine receptors mediating sedation in the mouse brain. Nature 264: 564-57, 1976.
4. Dickinson SL, Gadie B, Tulloch IF: $\propto_1$-and $\propto_2$-Adrenoreceptor antagonists differentially influence locomotor and stereotyped behavior induced by d-amphetamine and apomorphine in the rat. Psychopharmacology 96: 521-7, 1988.
5. Ferris RM, Cooper BR, Maxwell RA: Studies of bupropion's mechanism of antidepressant activity. J Clin Psychiat 44: 74-8, 1983.
6. Hamblin M, Creese I: Phenoxybenzamine discriminates multiple dopamine receptors- Eur J Pharmacol 65: 119-21, 1980.
7. Hyttel J: Functional evidence for selective dopamine D-1 receptor blockade by SCH 23390. Neuropharmacology 23: 1395-1401, 1984.
8. Marcais H, Protais P, Costentin J, Schwarts JC: A gradual score to evaluate the climbing behaviour elicited by apomorphine in mice. Psychopharmacology 56: 233-4, 1978.
9. Maxwell RA, Mehta NB, Tucker WEJR, Goldberg ME (ed). Schroeder DH, Stern WC: Bupropion. In: Pharmacological and Biochemical Properties of Drug Substances. Vol 3 American Pharmaceutical Association Academy of Pharmaceutical Sciences, Washington, D.C., 1981.
10. Moore NA, Axton MS: Production of climbing behavior in mice requires both D-1 and D-2 receptor activation. Psychopharmacology 94: 263-6, 1988.
11. Shore PA: Actions of amfonelic acid and other non-amphetamine stimulants on the dopamine neuron. J Pharm Pharmacol 28: 855-7, 1976.
12. Stoof JC, Kebabian JW: Two dopamine receptors: biochemistry, physiology, and pharmacology. Life Sci 35: 2281-96, 1984.
13. Soroko FE, Mehta NB, Maxwell RA, Ferris RM, Schroeder DH: Bupropion hydrochloride (±) ∝-t-butylamino-3-chloropropiophene HCL: a novel antidepressant agent. J Pharm Pharmacol 29: 767-70, 1977.
14. Walton KG, Liepmann P, Baldessarini RJ: Inhibition of dopamine-stimulated adenylate cyclase activity by phenoxybenzamine Eur J Pharmacol 52: 231-4, 1978.
15. Weisman A, Koe BK, Tenen SS: Antiamphetamine effects following inhibition of tyrosine hydroxylase. J Pharm Exp Ther 151: 339-52, 1966.
16. Zarrindast MR, Pousti A, Danesh-Kazemi M: Dopamine indirect properties of bupropion, Iuphar 9th International Congress of Pharmacology, London, p. 1179, 1984.
17. Zarrindast MR, Hosseini-Nia T: Anorectic and behavioral effects of bupropion. Gen Pharmacol 19: 201-4, 1988.
18. Zarrindast MR, Shahed-Dirin K: Bromocriptine induces climbing: possible D-1 or D-2 dopamine receptor involvement. Psychopharmacology 100: 275-80, 1990.